Influence of Size, Shape, Heteroatom Content and Dispersive Contributions on Guest Binding in a Coordination Cage

Susanne Löffler,[a] Axel Wuttke,[b] Bo Zhang,[a] Julian J. Holstein,[a] Ricardo A. Mata*[b] and Guido H. Clever*[a]

A halide-triggered metallosupramolecular host was systematically studied for the uptake of small neutral molecules by NMR and MS experiments. Starting from benzene, cyclic guests were screened with respect to size (ring count), shape (flatness, 3D structure, substitution pattern, flexibility) and hetero atom content (number, position, donor character). 5-rings and substituted 5/6-rings bind only weakly, while oversized (e.g. naphthalene, adamantane, ferrocene) and linear alkanes do not bind at all. Bridged 6-rings of the norbornane type and in particular DABCO bind strongly, likewise other guests with oppositely arranged hetero atoms. For the DABCO complex, a single crystal X-ray structure was obtained. The contribution of dispersive interactions to binding was derived from electronic structure calculations. Together, experimental and theoretical data deepen the understanding of guest selectivity and encapsulation driving force towards application of the host as switchable receptor and reaction chamber.

Non-covalent binding of small molecular guests inside the nanoscopic cavities of natural or artificial hosts such as enzymes or supramolecular cavitands is far from being fully understood. For example, the roles of shape match, conformational restrictions, steric repulsion vs. dispersive attraction as well as desolvation processes are still under debate.[1] Synthetic supramolecular chemistry is able to supply a plethora of container systems of variable size, shape and chemical makeup as model systems helping to understand non-covalent binding in nature.[2] In addition, tailor-made supramolecular architectures show potential as selective receptors,[3] waste sequestration agents,[4] nano-sized reaction chambers[5] and materials for molecular electronics.[6] In particular, the metal-mediated self-assembly of coordination cages[7] under modular variation of ligand scaffolds and functionalities has yielded sophisticated bottom-up nano systems such as switchable receptors,[8] selective catalysts,[9] and light-driven charge separators.[10]

Guest binding in these system has been studied intensively with ionic guests being of opposite charge than the cage, where Coulombic interactions dominate the driving force for encapsulation.[11] Less explored is the binding of neutral guest species inside ionic cages.[12] Here, solvophobic effects together with enthalpically beneficial host-guest contacts seem to play a major role but further systematic experimental and theoretical efforts are required to shed light on the situation in selected hosts. Recently, we reported an interpenetrated double cage[13] featuring three consecutive binding pockets, filled with tetrafluoroborate anions, that can be activated by the addition of chloride anions to bind neutral guest molecules such as benzene, cyclohexane and norbornadiene (Figure 1).[14]

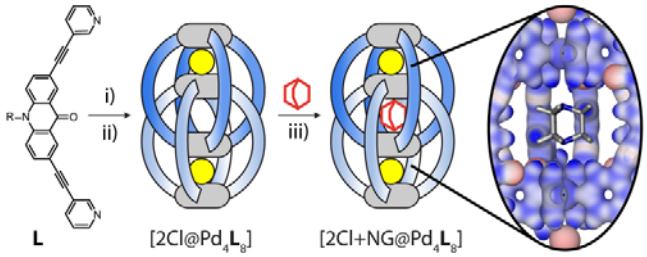

Fig. 1 Ligand structure, cage assembly, chloride activation and uptake of neutral guests. (i) $[Pd(CH_3CN)_4](BF_4)_2$ in CH_3CN; (ii) 2 eq. Cl^-; (iii) neutral guest. The inset shows the guest DABCO binding inside the central cavity (electrostatic potential mapping).

While the effect of halide binding has been well explained as an allosteric contraction of the whole architecture along the Pd_4-axis,[15] thereby shrinking the size of the outer pockets and expanding the inner pocket, the observed binding of neutral guests remained poorly understood in terms of driving force, structural preferences and scope. Herein, we deliver a systematic study comprising more than 50 small neutral guest molecules that reveals the influence of the guests' size, shape and chemical nature on the binding affinity.[16] In addition,

[a] *Department of Chemistry and Chemical Biology, TU Dortmund University, Otto-Hahn Str. 6, 44227 Dortmund, Germany. E-mail: guido.clever@tu-dortmund.de*
[b] *Institute for Physical Chemistry, Georg-August-University Göttingen, Tammannstr. 4, 37077 Göttingen, Germany*

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electronic structure calculations were conducted to obtain insights into the contribution of dispersive interactions.

Table 1 Experimental and computed binding free enthalpies, dispersive contributions, volumes and packing coefficients for selected guests (solvent: acetonitrile).

Guest	M / $gmol^{-1}$	V / $Å^3$ [a]	PC / % [b]	ΔG^{296} [c]	ΔG_{theo} [c]	ΔE_{disp} [c]
furan	*68.1*	*77.7*	*39*	*– 6.1*	1.4	*– 77.6*
cyclopentane	70.1	95.2	48	– 12.8	– 19.5	– 88.6
benzene	78.1	99.0	50	– 17.4	– 34.9	– 86.0
cyclohexane	84.2	111.8	56	– 20.2	– 18.9	– 107.1
norbornadiene	92.1	113.2	56	– 20.2	– 28.4	– 110.5
phenol	94.1	106.8	53	– 12.8	– 13.1	– 100.5
cyclooctane	112.2	147.2	74	– 15.6	---[d]	---[d]
DABCO	112.2	126.4	64	– 27.1	– 31.0	– 134.4

a: CPK volume of EDF2/6-31G optimized model; b: see reference 17 and the ESI†; c: in kJ/mol; d: not computed, see text for details.*

Binding free enthalpies between –6.1 kJ/mol (furan) and –27.1 kJ/mol (DABCO) were determined in acetonitrile by NMR signal integration of the free and filled host species present in the equilibrated samples at 296 K in the slow exchange regime (Table 1; [host] = 0.3 mM, [guest]/[host] see ESI†, equilibration time typically between 3-20 d). Figure 2 relates the obtained free enthalpies of binding to the guest volume and its packing coefficient (PC) in the cavity, respectively.[17] While oversized and non-cyclic guests were found to refrain from encapsulation (ESI†, Figures SI 1-5), smaller 5-ring guests bind weakly (PC between 39 and 48%) as do more voluminous guests carrying substituents such as a methyl group or oxygen atom. Among the 6-ring guests, a competition experiment revealed that benzene binds faster than cyclohexane while the latter binds stronger (Figure 2c). Interestingly, bridged 6-rings such as norbornadiene and its relatives bind rather strongly, showing that a 3-dimensional extension of the guest structure is not detrimental to encapsulation as long as the overall size does not increase beyond a PC of 74% (adamantane, for example, is not encapsulated; tentative PC = 81%).[18] Among the strongest binders, we found guests carrying two heteroatoms in opposite positions such as 1,4-pyrazine, 1,4-piperazine and 1,4-dioxane. Comparison of the latter guest to its 1,3-isomer is particularly intriguing since it demonstrates that the relative positioning of the heteroatoms is of paramount importance for strong binding, most likely due to the perfect orientation of the hetero atoms' lone pairs towards the two cationic Pd(II) centres lining the cavity. The latter explanation was further supported by a single crystal X-ray structure of the cage carrying its strongest binding guest DABCO (1,4-diazabicyclo[2.2.2]octane) in its central pocket (Figure 3a). While the fourfold crystallographic symmetry of the structure along the Pd_4-axis complicated the modelling of the axially disordered D_{3h}-symmetric guest, the DABCO molecule could be unambiguously refined to stand upright inside the cavity with its N_2-axis indeed coinciding with the cage's Pd_4-axis (Figure 3b, top). It is interesting to compare this binding mode with the orientation of the previously reported benzene-containing complex[14] in which the benzene molecular plane is oriented perpendicular to the Pd_4-axis, thereby exposing its π-surfaces towards the Pd(II) complexes (Figure 3b, bottom).

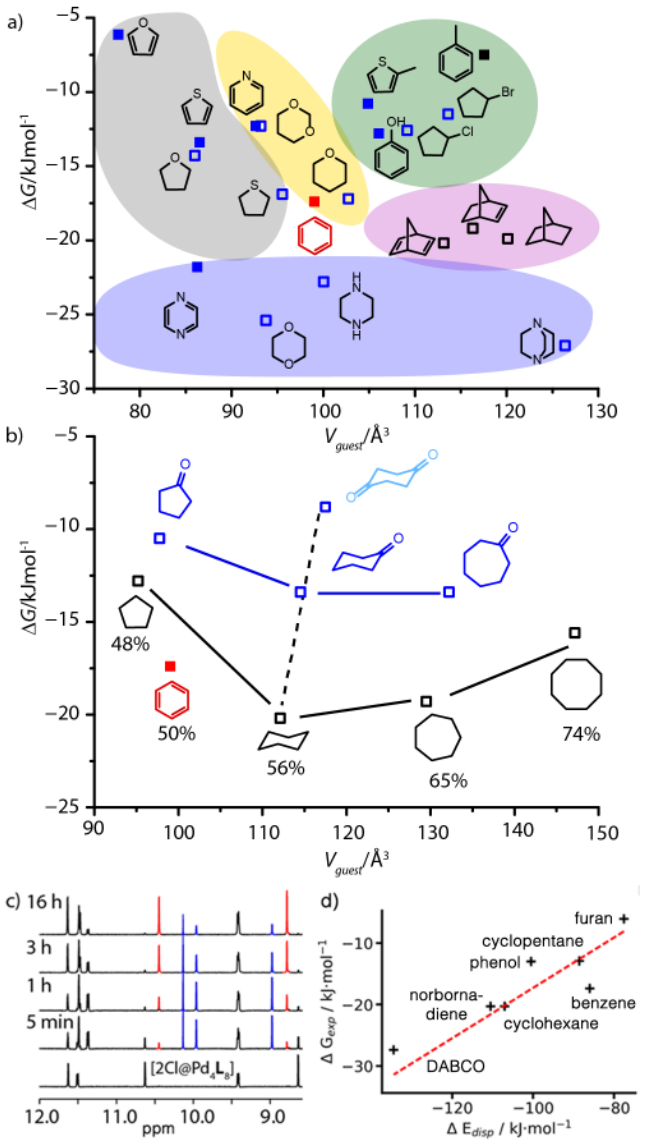

Fig. 2 Binding free enthalpies over guest volume for (a) various guest families with different ring sizes, 3D structure and hetero atom content and (b) selected series of cyclic alkanes and alkanones (packing coefficients are shown for the alkanes; solvent: acetonitrile). c) Temporal evolution of ^{1}H NMR spectra (500 MHz, 296 K, CD_3CN) from the competitive binding of simultaneously added benzene (blue) and cyclohexane (red; 20 eq. each) where benzene binds faster but cyclohexane stronger. d) Correlation of experimental guest affinities listed in Table 1 with computed dispersion contributions.

A further trend was observed when comparing the affinity/volume relationships for a series of cycloalkanes (C_5-C_8), cyclic ketones (C_5-C_7) and 1,4-cyclohexanedione (Figure 2b; note that cyclobutanone does not bind; ESI†). Here again, the addition of substituents leads to a decrease in binding affinity, demonstrating that lateral expansion of the oblate guest dimension is disfavoured with respect to bridging above the ring plane. Furthermore, the ring size effect is nicely reflected in these series. Small 5-rings bind weaker than their 6-ring siblings but further ring expansion leads to a decrease in

affinity. Nevertheless, voluminous cyclooctane (PC = 74%) still binds with considerable affinity, which we denote to its structural flexibility, allowing the guest to adopt a favourable conformation inside the cage.

Electronic structure calculations were carried out on a selected set of guest molecules and the host structure. In order to make the calculations amenable, a model of the double cage was used, whereby only the inner pocket was represented (ESI†, Fig. SI 33). Still, the total system size is beyond 300 atoms. For each guest, different orientations were sampled at the DFT level, followed by optimization with a frozen cage geometry. This approximation builds on the assumption that the chloride interaction in the outer pockets is much stronger than the binding in the inner pocket and thus rules the host geometry. We were unable to fit the cyclooctane guest within the fixed cage geometry and were therefore unable to carry out the calculations in this particular case.

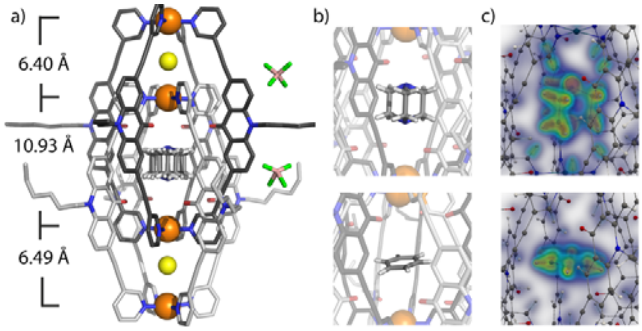

Fig. 3 Single crystal X-ray structure of $[2Cl+DABCO@Pd_4L_8]^{6+}$ (CCDC: 1557039; solvents and most counter anions outside the cage structure omitted): (a) full side view with disordered DABCO guest; (b) central pocket with one selected guest orientation and (c) calculated dispersion interaction density (DIDs) profile of DABCO (top) compared to benzene (bottom; from X-ray structure $[2Cl+benzene@Pd_4L_8]^{6+}$; CCDC 1035009).[14] (Colour coding: red = strong; blue = weak interacting regions).

From the optimised structures, we calculated at the SCS-LMP2/cc-pVTZ level (with an effective core potential for Pd)[19] the dispersion interactions between host and guest. Some of the results are provided in Table 1 (ΔE_{disp}), and exemplary dispersion interaction density (DID)[20] profiles for DABCO and benzene are shown in Fig. 3c (for further data see Fig SI 34 in the ESI†). As expected, these contributions increase with system size, with the 5-ring guests in the range of 70-90 kJ/mol, and the 6-rings going beyond 100 kJ/mol. It should be noted that given the close contacts between the host and the guest, the DFT D3 corrections[21] cannot be used to interpret the forces at play. The latter go well beyond 300 kJ/mol, which is not realistic for the type of systems under study.

The DID profile shows that close C-H contacts to the interior of the pocket dominate the dispersion profile. This is observed also in other systems, somewhat reminiscent of coupled diamondoids.[20,22] Individually, these are all small contributions, but they significantly add up. It also explains the difference in ΔE_{disp} between benzene and cyclohexane, since the latter has a larger number of C-H contacts. Interestingly, the dispersion itself correlates with the experimental binding affinity for the subset of guests which were computed (Figure 2d and Table 1). The slope of the least-squares fit is 0.41, reflecting the attenuation from solvent effects (i.e. stabilising dispersion contacts with solvent in the unbound state). A comparison of binding enthalpies of the guest pair benzene/cyclohexane from solvents acetonitrile/acetone revealed a differential contribution of desolvation, with more detailed investigations currently underway.

In addition, we devised a composite approach for the calculation of the free enthalpy of binding (the procedure is detailed in the ESI†). In general, the computed values agree well with the experimental estimates, the only outlier being benzene. The mean absolute deviation of the computed binding affinities is 6.5 kJ/mol (4.6 kJ/mol excluding benzene), which is expectable given the size and complexity of the system.[23] Nevertheless, we hope to further refine our computational approach in the future, in particular allowing for a relaxation of the binding pocket.

In conclusion, our study curtails the scope of neutral guest molecules that can be encapsulated by the chloride-triggered interpenetrated host system. In terms of size and shape, 6-rings and norbornene-type compounds are favoured. One substituent in the size of a methyl group is tolerated (leading to a drop in affinity) but two substituents are not. The opposite arrangement of hetero atoms in bridged or unbridged 6-ring guests is favourable, indicating that orientation of lone pairs towards both cationic Pd(II) centres leads to a stabilizing two-point attachment. This assumption was supported by the X-ray structure of the $[2Cl+DABCO@Pd_4L_8]^{6+}$ host-guest complex. Electronic structure calculations reveal that binding is strongly favoured by dispersion interactions. Our ongoing experimental and theoretical work is dedicated at dissecting the observed affinities into enthalpic and entropic contributions[24] and comparing binding in different solvents.[25] The herein reported findings form the basis for the further utilization of this stimuli-responsive system for selective recognition and tuneable catalysis.

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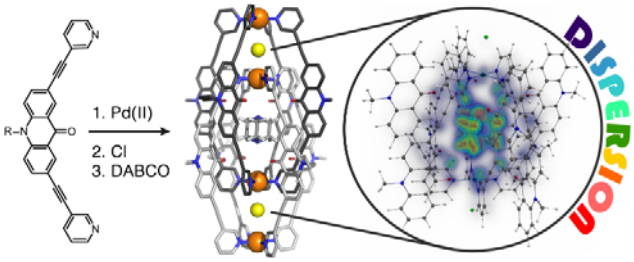

Encapsulation of neutral guest molecules inside a self-assembled coordination cage was systematically studied by NMR and MS experiments. Electronic structure calculations reveal substantial contributions of dispersive interactions to binding.